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Association between chronic asymptomatic pancreatic hyperenzymemia and pancreatic ductal anomalies: a magnetic resonance cholangiopancreatography study

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Abstract

Purpose Elucidating the association between pancreatic ductal anomalies and chronic asymptomatic pancreatic hyperenzymemia using magnetic resonance cholangiopancreatography.

Methods We conducted a single-center, retrospective, case–control study. The healthy community group comprised 554 subjects who participated in a paid, whole-body health checkup program. The patient group comprised 14 subjects with idiopathic pancreatic hyperamylasemia or hyperlipasemia. All subjects underwent magnetic resonance cholangiopancreatography. The clinical features and incidence rates of pancreatic ductal anomalies were then compared between the groups.

Results Compared to the healthy community group, the patient group was significantly more likely to be ≥ age 65 (71.4% of patient group vs. 22.1% of healthy community group), have a history of diabetes mellitus (21.4% vs. 5.4%) or hypertension (35.7% vs. 11.4%), and to have pancreas divisum (21.4% vs. 2.7%), meandering main pancreatic duct (21.4% vs. 4.1%), Wirsungocele (14.3% vs. 1.1%), or dilated main pancreatic duct (14.3% vs. 2.3%). Multivariate analysis found that age ≥ 65 (odds ratio 8.76), presence of pancreas divisum (odds ratio 13.2), meandering main pancreatic duct (odds ratio 8.95), and Wirsungocele (odds ratio 17.6) were independent factors significantly associated with chronic asymptomatic pancreatic hyperenzymemia.

Conclusions Pancreas divisum, meandering main pancreatic duct, and Wirsungocele were independently associated with chronic asymptomatic pancreatic hyperenzymemia.

Keywords Amylase · Lipase · Magnetic resonance imaging · Pancreatitis

Introduction

Chronic asymptomatic pancreatic hyperenzymemia (CAPH), or chronic non-pathological pancreatic hyperenzymemia, is a pathological condition in which chronic serum hyperamylasemia or hyperlipasemia is observed without a specific etiology [1]. Previous studies reported that hyperenzymemia is related to pancreas divisum, the most prevalent congenital pancreatic ductal anomaly, occurring in up to 6.0% of American and European individuals and 1.5% of Asian individuals [2–4]. Pancreas divisum is strongly associated with the onset of idiopathic acute and recurrent pancreatitis [5]. The second, most prevalent pancreatic ductal anomaly is a recently reported condition called meandering main pancreatic duct (MMPD). MMPD involves abnormal curvature of the main pancreatic duct in the pancreatic head and can be classified as the loop type or reverse-Z type [6]. In Japanese populations, MMPD's prevalence is reported to be 2.2% [6]. Both MMPD and pancreas divisum are associated with idiopathic acute and recurrent pancreatitis [6]. There are no guidelines nor an evidence-based indication on the best imaging modality to assess CAPH [7]. CAPH patients commonly undergo repeated medical evaluations to rule out pancreatic diseases. Such use of medical resources could be reduced if the benign pathological conditions that cause CAPH were more clearly elucidated. However, the relationship between CAPH and pancreatic ductal anomalies, other than pancreas divisum, has not been assessed previously.

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Thus, the present study aimed to elucidate the association between pancreatic ductal anomalies and CAPH using magnetic resonance cholangiopancreatography.

Materials and methods

Our Institutional Review Board approved this STROBE-compliant, single-center, retrospective case–control study and waived informed consent. All experiments and methods were performed in accordance with the Declaration of Helsinki.

Healthy community group

The study included a healthy community group and a CAPH group. The healthy community group comprised consecutive subjects who participated in a paid, whole-body health checkup program at our hospital between October 12, 2006 and May 31, 2007 that was advertised via leaflets and the Internet. The program included general blood tests, including serum amylase, abdominal magnetic resonance (MR) imaging, magnetic resonance cholangiopancreatography (MRCP), a review of smoking and drinking habits, medical history, an interview on subjective symptoms, and a physical examination performed by a physician. All tests for individual subjects were performed on the same day. Only subjects who underwent all of the above-mentioned examinations were included in this study. The exclusion criteria for the healthy community group were as follows: medical history of pancreatic disease, inadequate MR image quality for evaluating the pancreatic duct in the pancreatic head, post-pancreaticoduodenectomy status, presence of a pancreatic tumor or biliary tumor in the pancreatic head, and hyperamylasemia (above the upper limit of the reference range). The flow chart of subject selection is depicted in Fig. 1a.

CAPH group

The CAPH group included consecutive patients who visited our hospital's Department of Gastroenterology and underwent abdominal MR imaging and MRCP for detailed examination of CAPH between January 1, 2010 and September 30, 2015. CAPH was defined according to the following established criteria [2, 8, 9]: (1) pancreatic hyperamylasemia and/or hyperlipasemia lasting more than 6 months, (2) asymptomatic presentation (free from abdominal pain or back pain), and (3) idiopathic presentation (no apparent cause of hyperenzymemia identified after close medical checkup). The exclusion criteria were as follows: incomplete clinical evaluation, inadequate quality of MR images for evaluating the pancreatic duct in the pancreatic head, medical history of pancreatic disease, diagnosis of pancreatic disease, post-pancreaticoduodenectomy status, and the presence of extra-pancreatic disease (hepatitis viral infection, status after post-liver plantation, Sjogren syndrome, etc.) or history of drug use that could induce hyperamylasemia or hyperlipasemia. We performed a retrospective medical chart review of all patients suspected of having CAPH and recorded the maximum levels of serum amylase, pancreatic amylase, and lipase. The durations of pancreatic hyperamylasemia and/or hyperlipasemia were also recorded. If serum pancreatic amylase and/or lipase levels normalized during the observation period, the highest levels were recorded. The flow chart of CAPH patient selection is depicted in Fig. 1b.

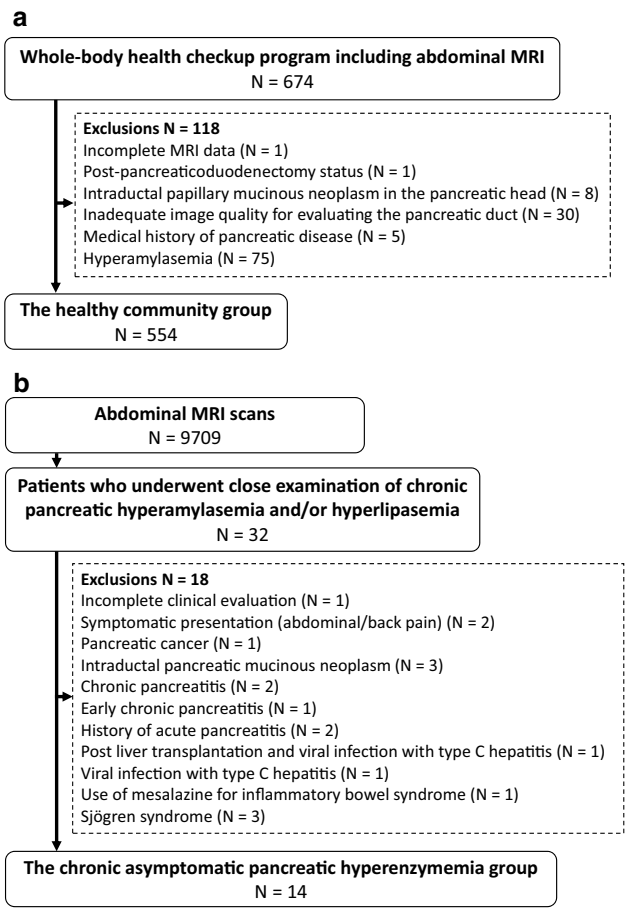

Fig. 1 Subject selection flow chart for **a** the healthy community group and **b** the chronic asymptomatic pancreatic hyperenzymemia group

MR imaging technique

In the healthy community group, MR imaging was performed using 3T scanners (GE Medical Systems, Waukesha, WI). MRCP were acquired in the coronal plane, during breath-hold, using a two-dimensional half-Fourier fast spin echo technique (repetition time [TR]/echo time [TE] = ∞/600 ms; slice thickness [ST] = 40 mm). Coronal

and oblique-coronal projection images were reconstructed. Additionally, transaxial fast spin echo T2-weighted images and fat-suppressed T1-weighted images were acquired using a three-dimensional gradient echo technique. No premedication was administered. In the CAPH group, MR imaging was performed using 3T (GE Medical Systems) or 1.5T scanners (GE Medical Systems; Siemens AG, Erlangen, Germany; Toshiba Medical Systems, Tochigi, Japan). MRCP were acquired during breath-hold using two-dimensional half-Fourier fast spin echo (TR/TE = 2400–∞/600–1100 ms; ST = 30–50 mm) and respiratory-gated three-dimensional half-Fourier fast spin echo (TR/TE = 1300–∞/500–900 ms; ST = 1.2–2.0 mm with no gap) techniques. Coronal and oblique-coronal projection images were reconstructed. Transaxial and coronal T2-weighted images and fat-suppressed T1-weighted images were also acquired. Manganese chloride solution (Bothdel Oral Solution 10; Kyowa Hakko Kirin, Tokyo, Japan) was administered as a negative oral contrast agent before MR imaging.

Image interpretation

All MR images were interpreted on picture archiving and communication system workstations (Centricity; GE Medical Systems) by two board-certified abdominal diagnostic radiologists with 7 and 12 years of experience in pancreaticobiliary imaging who were blinded to the clinical conditions. The radiologists independently determined the presence or absence of pancreas divisum, MMPD, Wirsungocele, Santorinicele, and other radiological findings. In line with previous work [5], pancreas divisum was considered present if the oblique-coronal MRCP plane image showed that (1) the dorsal pancreatic duct was dominant in the pancreatic head and coursed the ventral side of the common bile duct, finally terminating at the minor papilla, and (2) the dorsal duct was thicker than the ventral duct in the pancreatic head (Fig. 2a). MMPD was considered present [6] if the oblique-coronal MRCP plane image showed that (1) the MPD curve in the pancreatic head had two or more extrema in the direction vertical to the body axis, forming a curve or angle resulting in a localized loop (loop type) or reverse-Z shaped hairpin (reverse-Z type), and (2) the MPD curve was not accompanied by anomalous arrangement of the pancreaticobiliary ductal system or pancreas divisum (complete or incomplete) (Fig. 2b). Wirsungocele was diagnosed when cystic dilatation was observed at the terminal part of the duct of Wirsung (Fig. 2b and c) [10]. Santorinicele was diagnosed when cystic dilatation was observed at the terminal part of the duct of Santorini [11]. The radiologists also recorded any other radiographic findings related to the pancreaticobiliary system, e.g., other pancreatic ductal fusion variants, pancreatic cystic lesions, pancreatic ductal/ductile dilatation or irregularity on MRCP, pancreatic parenchymal abnormality, or juxtapapillary duodenal diverticulum on T1- and T2-weighted images. If either radiologist found the pancreatic ductal

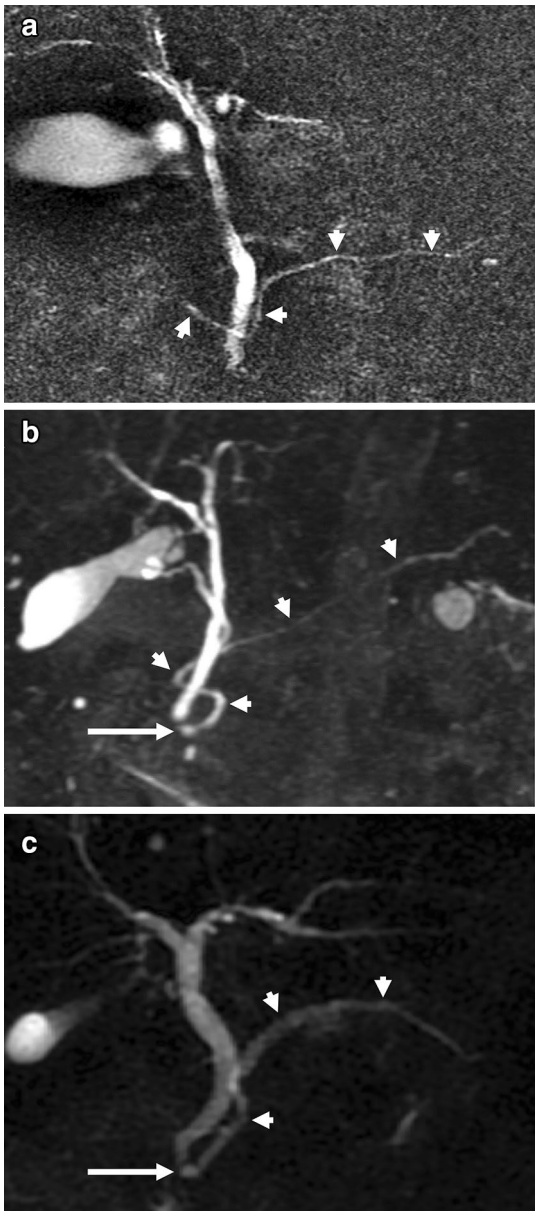

Fig. 2 Magnetic resonance cholangiopancreatography of **a** a 74-year-old woman with asymptomatic pancreatic hyperamylasemia showing complete pancreas divisum (case 5, two-dimensional half-Fourier fast spin echo); **b** a 57-year-old woman with both asymptomatic pancreatic hyperamylasemia and hyperlipasemia, showing Wirsungocele accompanied by a reverse-Z-type meandering main pancreatic duct (case 2, three-dimensional half-Fourier fast spin echo); and **c** a 69-year-old woman with both asymptomatic pancreatic hyperamylasemia and hyperlipasemia, showing Wirsungocele accompanied by dilated main pancreatic duct (4 mm) (case 7, two-dimensional half-Fourier fast spin echo). Short arrows indicate the main pancreatic duct. The long arrows indicate Wirsungocele

anatomy indeterminable on these images, those cases were excluded because of poor image quality. If the diagnoses differed between the two radiologists, consensus was achieved by joint reading of the images.

Statistical analysis

The clinical background and incidence of radiological findings were compared between the healthy community group and the CAPH group. For univariate comparisons between groups, we used Welch's *t*-test for continuous variables and Fisher's exact test for categorical variables. All categorical variables and age ≥ 65, Brinkman index ≥ 600, and alcohol intake ≥ 20 g/day of the continuous variables were considered potential risk factors for CAPH. For multivariate comparisons, multiple logistic regression analysis was used to identify factors independently associated with CAPH among the categorical variables that were significant in univariate analysis. To avoid issues related to multicollinearity, only super-type categorical variables were included in the multivariate analysis. We used Cohen's coefficient kappa (κ) to assess interrater reliability of the diagnosis of pancreatic ductal anomalies. The level of statistical significance was set at $P < 0.05$. The free software R ver. 2.9 (R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org/) was used for all statistical analyses.

Results

The final healthy community group comprised 554 subjects (mean age, 56.1 years; standard deviation (SD), 10.1). There were 329 male subjects (age range 40–82 years; mean age 55.8 years) and 225 female subjects (age range 40–84 years; mean age 56.5 years). The mean Brinkman index (cigarettes/day × year), alcohol intake (g/day), and serum amylase level (U/L) were 256 (SD 419), 2.2 (SD 2.9), and 87.9 (SD 21.3), respectively. The final CAPH group comprised 14 subjects (mean age 67.6 years; SD 10.9). There were seven male subjects (age range 58–83 years; mean, 69.4 years) and seven female subjects (age range 40–78 years; mean 65.9 years) (Table 1). No subjects in the CAPH group were related. The mean Brinkman index (cigarettes/day × year), alcohol intake (g/day) and maximum serum amylase level (U/L) during clinical course were 11 (SD 43), 0.7 (SD 1.3), and 255 (SD 100), respectively. Table 1 presents the radiological and serological data for subjects in the CAPH group. In all 14 subjects, pancreatic hyperamylasemia and/or hyperlipasemia were incidental findings on blood tests. In the CAPH group, the average Brinkman index and alcohol intake were both lower than those in the healthy community group (Welch's *t*-test, $P < 0.001$ for both tests). The average maximum serum amylase level during the clinical course was significantly higher than that in the healthy

Table 1 Characteristics of subjects in the chronic asymptomatic pancreatic hyperenzymemia (CAPH) group

Case	Age	Sex	Radiological findings	AMY (U/L)	PAMY (U/L)	LPS (U/L)	PH	Duration (months)	Familial history
1	73	F	Z-MMPD	429*	127*	105*	Yes	96	No
2	57	F	Z-MMPD, Wirsungocele	325*	320*	575*	Yes	96	No
3	70	F	Z-MMPD	429*	70*	120*	Yes	96	No
4	78	F	Complete PD	265*	85*	41	Yes	144	No
5	74	F	Complete PD	327*	201*	N/A	Yes	12	Pancreatic cancer (brother)
6	77	M	Incomplete PD	187*	97*	53*	Yes	12	No
7	69	F	Wirsungocele, Dilated MPD (4.0 mm)	N/A	53*	74*	Yes	7	No
8	61	M	FDBD, cyst	227*	112*	545*	Yes	24	No
9	40	F	FDBD	210*	86*	61*	Yes	120	No
10	58	M	Dilatated MPD (4.5 mm)	145*	N/A	62*	Yes	12	No
11	68	M	Irregularity of MPD	98	42*	62*	Yes	36	Pancreatitis (son)
12	68	M	None	249*	217*	210*	Yes	132	No
13	83	M	None	243*	275*	N/A	Yes	192	No
14	71	M	None	183	101	99	Yes	54	No
Mean [standard deviation]				255.2 [96.2]	137.4 [84.3]	167.3 [181.0]		69.7 [57.4]	

Normal range (U/L): serum amylase, 44–132; serum pancreatic amylase, 14–41; serum lipase, 13–49

AMY serum amylase, *FDBD* focal dilatation of the branch ducts, *LPS* serum lipase, *MPD* main pancreatic duct, *PAMY* serum pancreatic amylase, *PD* pancreas divisum, *PH* pancreatic hyperamylasemia, *Z-MMPD* reverse-Z type meandering main pancreatic duct, *N/A* not available

*Above upper limit of normal range (indicating hyperamylasemia)

Table 2 Results of univariate and multivariate analyses to identify factors associated with chronic asymptomatic pancreatic hyperenzymemia

Variable	Community	CAPH	Univariate analysis[a]		Multivariate analysis[b]	
	(*N* = 554)	(*N* = 14)	*P*	Odds ratio [95% CI]	*P*	Odds ratio [95% CI]
Clinical feature						
Age (≥ 65)	123 [23]	10 [71]	< 0.001*	8.76 [2.70–28.4]	< 0.001*	11.5 [3.13–42.3]
Female	225 [41]	7 [50]	0.58			
BI (≥ 600)	100 [18]	0 [0]	0.15			
Alcohol intake (≥ 20 g/day)	0 [0.0]	0 [0.0]	1			
Diabetes mellitus	30 [5]	3 [21]	0.04*	4.76 [1.26–18.0]	0.20	
Hypertension	63 [11]	5 [36]	0.02*	4.33 [1.41–13.3]	0.19	
Malignant neoplasm	35 [6]	1 [7]	1			
Autoimmune disease	11 [2]	0 [0]	1			
Radiological feature						
Pancreas divisum	15 [3]	3 [21]	0.01*	9.80 [2.48–38.8]	< 0.001*	13.2 [2.69–64.4]
Complete type	14 [3]	2 [14]	0.06			
Incomplete type	1 [0]	1 [7]	0.049*	42.5 [2.52–718]		
MMPD	23 [4]	3 [21]	0.02*	6.30 [1.64–24.1]	0.01*	8.95 [1.85–43.4]
Reverse-Z type	15 [3]	3 [21]	0.01*	9.80 [2.48–38.8]		
Loop type	8 [1]	0 [0]	1			
Ansa pancreatica	4 [1]	0 [0]	1			
Long common duct (8–15 mm)	1 [0]	0 [0]	1			
Retroportal MPD	1 [0]	0 [0]	1			
Wirsungocele	6 [1]	2 [14]	0.01*	15.2 [2.78–83.3]	0.01*	17.6 [2.10–148]
Bifid MPD	1 [0]	0 [0]	1			
Cystic lesion	74 [13]	1 [7]	1			
Suspected IPMN	13 [2]	0 [0]	1			
Dilated MPD	13 [2]	2 [14]	0.049*	6.94 [1.41–34.2]	1	
FDBD	13 [2]	0 [0]	1			
Irregularity of MPD	5 [1]	1 [7]	0.14			
Choledochal cyst	1 [0]	0 [0]	1			
Hypogenesis of the pancreatic tail	1 [0]	0 [0]	1			
Juxtapapillary diverticulum	8 [1]	0 [0]	1			

Data are presented as *N* (%) unless otherwise indicated

BI Brinkman index (cigarettes/day × year), *CI* confidential interval, *CAPH* chronic asymptomatic pancreatic hyperenzymemia, *FDBD* focal dilatation of the branch ducts, *IPMN* intraductal pancreatic mucinous neoplasm, *MMPD* meandering main pancreatic duct, *MPD* main pancreatic duct, *N/A* not applicable, *SD* standard deviation

[a]Fisher's exact test

[b]Multiple logistic regression analysis

*Statistically significant

community group (Welch's *t*-test, $P < 0.001$). Table 2 presents and compares the clinical background and radiologic findings for the healthy community group and CAPH group. Of the 14 subjects in the CAPH group, 11 (78.6%) had one or more pancreatic findings and 7 (50.0%) had pancreatic ductal anomalies (pancreas divisum, MMPD, and Wirsungocele) (Table 1). Of the 554 subjects in the healthy community group, 288 (52.1%) had one or more pancreatic findings, and 50 (9.0%) had pancreatic ductal anomalies (Table 2). Univariate analyses revealed age ≥ 65, diabetes mellitus, hypertension, pancreas divisum, MMPD, Wirsungocele, and dilated main pancreatic duct as possible CAPH risk factors (Table 2). Subsequent multiple logistic regression analysis revealed significant positive associations of pancreas divisum, MMPD, Wirsungocele, and age ≥ 65 with CAPH. Interrater reliability for diagnosing pancreatic ductal anomalies was excellent: κ value (agreement ratio) for overall pancreatic ductal anomalies, pancreas divisum, MMPD, and Wirsungocele were 0.93 (98.9%), 0.89 (99.5%), 0.93 (99.5%), and 1.00 (100%), respectively.

Discussion

Using MRCP, this retrospective case–control study revealed significantly higher prevalence rates of pancreas divisum, MMPD, and Wirsungocele in the CAPH group than the healthy community group. Further, these pancreatic ductal anomalies were independently associated with CAPH onset.

The incidences of pancreatic ductal anomalies in our healthy community group are consistent with previous reports [2–4, 12]. In the CAPH group, 78.6% of subjects had one or more abnormal findings on MRCP. This proportion is relatively higher than that of a previous meta-analysis of 43.3% [7, 13, 14]. This could be because more pancreatic findings were included in image interpretation in the present study such as MMPD and Wirsungocele. By contrast, Gullo et al. reported that only 9.5% of subjects with CAPH had pancreatic ductal anomalies on MRCP and assumed that pancreatic ductal anomalies were less responsible for CAPH [15]. This difference could be due to differences in settings, including the use of secretin for MRCP in previous studies, differences in the inclusion criteria for CAPH or pancreatic anomaly, and other abnormalities.

Pancreas divisum is reported to be associated with the onset of CAPH as well as pancreatitis—particularly idiopathic chronic and recurrent acute pancreatitis [2, 5, 16, 17]. The mechanism by which pancreas divisum induces CAPH and pancreatitis may involve congestion of pancreatic juice drainage, as drainage of pancreatic juice is greater via the relatively small accessory pancreatic duct papilla than the ampulla of Vater [2, 16, 17]. Recently, mutation of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene was reported to have a strong relationship with the onset of pancreatitis and expression of pancreas divisum, and this mutation was observed in about 47% of patients with pancreatitis accompanied by pancreas divisum [18]. The *CFTR* gene mutation presumably increases the viscosity of pancreatic juice and causes pancreatitis [19]. However, the primary pathological mechanism (viscous pancreatic juice or a thin drainage route) that causes pancreatitis, accompanied by pancreas divisum, remains controversial [20]. In a separate study, Gullo et al. found that the frequency of *CFTR* gene mutations in subjects with CAPH was similar to the carrier frequency in the general population [21]. Based on these findings, pancreas divisum and idiopathic pancreatic hyperenzymemia might be associated with underlying gene expression.

Similarly, MMPD is associated with the onset of idiopathic recurrent acute pancreatitis [6]. Although the mechanism by which MMPD induces pancreatitis remains unclear, it may involve congestion of pancreatic juice drainage. The congestion occurs because of the main pancreatic duct's abnormal course, which is believed to originate through a fusion abnormality of the dorsal and ventral pancreatic ducts in the pancreatic head, as in other cases of pancreatic ductal anomalies [5, 6, 22]. However, to the best of our knowledge, there are no previous reports on the relationship between MMPD and CAPH. We were unable to clarify the mechanism by which CAPH occurs in subjects with MMPD in the present study. We speculate that latent genetic abnormalities, and/or impaired flow of pancreatic juice, might be associated with CAPH onset, which is assumed when MMPD is found to cause idiopathic recurrent pancreatitis [6]. Thus, further investigation of genetic abnormalities in subjects with CAPH accompanied with MMPD is needed.

Wirsungocele is a cystic dilatation of the terminal part of the Wirsung duct and is speculated to have a similar pathophysiology to Santorinicele [11]. Although previous case reports have associated Wirsungocele with acute pancreatitis and chronic abdominal pain, there is little evidence of this, and the mechanism and etiology have not been confirmed [10, 23]. To the best of our knowledge, no previous report has discussed the relationship between Wirsungocele and CAPH. Although the mechanism by which CAPH occurs in subjects with Wirsungocele was not clarified in the present study, we speculate that it is associated with increased intraductal pressure and/or congestion of pancreatic juice drainage, which is assumed when Santorinicele without pancreas divisum pathophysiology is related to pancreatitis [11].

In the present study, age ≥ 65 was independently related to CAPH, possibly because of selection bias, since hyperamylasemia and hyperlipasemia were incidentally detected during hospitalization or outpatient visits for other diseases in most CAPH group subjects. Age should not affect the incidence rates for pancreas divisum and MMPD since, with a few exceptions, they are considered congenital [5, 6, 24].

There are no established guidelines for the imaging assessment of CAPH. As those pancreatic ductal anomalies mentioned above were independently associated with CAPH, it would be reasonable that patients with CAPH undergo MRCP once to check pancreatic findings including pancreatic ductal anomalies and to exclude pancreatic diseases [7, 25, 26].

Limitations of the present study include a relatively small number of subjects in the CAPH group, its non-longitudinal but retrospective cross-sectional approach, and the absence of genetic screening.

In conclusion, the present study found that pancreatic ductal anomalies were independently associated with the onset of CAPH. In patients with CAPH, it might be important to check for pancreatic ductal abnormalities as a potential cause of CAPH.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to declare.

Ethical approval Our Institutional Review Board approved this STROBE-compliant single-center retrospective case–control study.

Informed consent Our Institutional Review Board waived informed consent for this STROBE-compliant single-center retrospective case–control study.

STROBE statement We confirm that this study is STROBE-compliant.

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